



FOOD AND DRUG ADMINISTRATION
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

MEMORANDUM

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Subject: *Final Review of CSL Behring's Stability Studies in the Biologics License Application for Coagulation Factor IX (Recombinant), Albumin Fusion Protein [IDELVION]*

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1. Executive Summary

On 4 December 2014, CSL Behring (CSLB) submitted an original biologics license application (BLA) for Coagulation Factor IX (Recombinant), Albumin Fusion Protein (rIX-FP). The proposed proprietary name of the product is IDELVION and the company code is CSL654.

rIX-FP is expressed in a Chinese Hamster Ovary (CHO) cell line by recombinant DNA technology using fusion of the genetic constructs of albumin and coagulation factor IX (FIX). The fusion protein is then purified using conventional (b) (4) processes. rIX-FP remains intact in the circulation until FIX is activated, whereupon the albumin moiety is cleaved off, releasing activated FIX (FIXa). rIX-FP final drug product (FDP) is provided as a lyophilized powder in single-use glass vials containing nominally 250, 500, 1000 or 2000 international units (IU) of rIX-FP.

rIX-FP is indicated in patients with hemophilia B (congenital FIX deficiency) for: (a) on-demand control and prevention of bleeding episodes; (b) perioperative management of bleeding; and (c) routine prophylaxis to prevent or reduce the frequency of bleeding episodes.

I reviewed the stability data for the bulk drug substance (BDS), FDP and sterile Water for Injection (sWFI) provided in the original BLA and amendments 32 and 44 dated August 14 and

November 5, 2015, respectively. The results and information on rIX-FP stability support the proposed shelf-life and dating periods for rIX-FP BDS, FDP and sWFI as follows:

- For rIX-FP BDS: (b) (4) .
- For rIX-FP FDP:
 - For 250 IU and 500 IU: 24 months at +5°C (±3°C) to +25°C (b) (4) (b) (4) protected from light.
 - For 1000 IU and 2000 IU: 36 months at +5°C (±3°C) to +25°C (b) (4) (b) (4), protected from light.
- The reconstituted product can also be stored at room temperature (25°C) for a maximum of 4 hours within the shelf-life.
- sWFI: (b) (4) .

The following storage conditions were investigated:

- (b) (4) .
- FDP: 5°C (±3°C) (b) (4) (proposed real-time storage condition) for 36 months, 25°C (b) (4) (proposed real-time storage condition) for 36 months, (b) (4) and reconstitution study at room temperature (max.+25°C) of samples that have been stored for (b) (4) .
- sWFI: (b) (4)
- (b) (4)
- FDP: The test parameters were appearance (pale yellow to white (b) (4) plug), visual inspection of solution (clear, colorless solution, free of visible particles), dissolution time: (b) (4) protein content (b) (4) (b) (4)), FIX coagulation activity (b) (4) (b) (4) FIX activity (b) (4) (b) (4) residual moisture (b) (4) and bacterial endotoxins (b) (4)

- (b) (4)

Conclusions and Recommendation:

My review of the stability studies confirmed that the manufacturing process is sufficiently established to manufacture the IDELVION product of consistent quality. I conclude that the stability data for BDS, FDP and sWFI support the proposed shelf-life and storage conditions:

- BDS for (b) (4)
- FDP 250 IU and 500 IU dosage for 24 months at +5°C (±3°C) to +25°C (b) (4), protected from light. FDP 1000 IU and 2000 IU dosage for 36 months at +5°C (±3°C) to +25°C (b) (4) / (b) (4), protected from light.
- The reconstituted FDP must be used immediately or within 4 hours after reconstitution.
- The shelf life of sWFI is (b) (4).

Under these storage conditions, there is no impact of storage on the strength, purity and quality of IDELVION BDS and FDP, and sWFI within the proposed shelf-life.

I recommend the approval of this submission.

2. Stability Study for Bulk Drug Substance

Stability studies are being conducted to assess the stability of the rIX-FP BDS and to demonstrate that the BDS will remain within specification during the defined shelf-life ((b) (4)) when stored at the proposed storage condition (b) (4).

a) Materials

(b) (4)

3 Pages determined to be not releasable: (b)(4)

(b) (4)

(b) (4)

3. Stability Study for Final Drug Product

CSLB performed stability study on pilot scale batches, engineering batches and GMP batches. CSLB provided three completed stability study reports (STR-809-PS-001A-01, STR 809-002-02 and REP-11554), two interim stability reports (STR-809-003/-006-02 and STR 809-008-2), and the statistical analysis (SR-809-008) and the study report (STR-809-PS-001A). In addition, the (b) (4) stability study report (STR-809-PS-001A) was included.

a) Materials

A total of (b) (4) batches were used for the stability study, which included (b) (4) batches of pilot scale and (b) (4) commercial scale batches. (b) (4) engineering batches and (b) (4) cGMP batches of FDP were included in the stability study, all of which were manufactured at CSLB in Emil-von-Behring-Strasse 76 D-35041 Marburg, Germany.

b) Specifications for FDP:

Table 2. FDP Parameters and Specifications for CSL654 Drug Product

Test	Testcode / Location in dossier	Specifications
(b) (4)	Quantity	(b) (4)
FIX coagulation Assay	Potency Identity	
Albumin by (b) (4)	Quality	
(b) (4)	Identity	
(b) (4)	Identity	
(b) (4)	Purity	
(b) (4)	Purity	
FIXa Assay	Purity	
(b) (4)	Purity	
(b) (4) FIX activity	Purity	
(b) (4)	Purity	
(b) (4)	Purity	
(b) (4) -visible particles by (b) (4)	Purity	

		(b) (4)
Endotoxin	Purity Safety	(b) (4)
Sterility	Safety	Pass if no contamination detected
Appearance by visual inspection (Lyophilized cake)	Quality	Pass if pale yellow to white (b) (4) cake
Residual water by (b) (4)	Quality	(b) (4)
(b) (4)	Quality	(b) (4)
Appearance by visual inspection (Dissolution time)	Quality	(b) (4)
Appearance by visual inspection (Appearance after reconstitution)	Quality	Pass if yellow to colorless clear liquid and free of visible particles
(b) (4)	Quality	(b) (4)
(b) (4)	Quality	(b) (4)
Polysorbate 80 by (b) (4)	Quality	(b) (4)
Mannitol by (b) (4)	Quality	(b) (4)
Sucrose by (b) (4)	Quality	(b) (4)
Determination of Trisodium Citrate b (b) (4)	Quality	(b) (4) (b) (4)

(b) (4)

c) FDP Storage Conditions

- Long-Term Condition: +5°C ($\pm 3^\circ\text{C}$) (b) (4)
+25°C (b) (4) (b) (4)
- (b) (4) Condition: (b) (4)
- Reconstitution, room temperature (max.+25°C)

d) Stability Study Results:

1) Pilot Scale Batches

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

3) Commercial GMP Batches

(b) (4) CSL654 GMP batches, including (b) (4) batches of each filing size, were initially enrolled in stability studies. Another batch was added later making it a total of (b) (4) CSL654 GMP batches enrolled in stability studies.

(b) (4)

Reviewer's comments: After 24 months storage, all tested data are within the specifications at storage condition 5 to 25 °C/(b) (4) for all batches of filling sizes 250, 500, 1000 and 2000 IU. A slight decrease of potency is observed when the product is stored at +25°C/(b) (4) (b) (4) (b) (4) an increase of (b) (4) a decrease of potency, a decrease of the (b) (4) measured by (b) (4) (b) (4) an increase of the residual moisture content were detected.

- Reconstitution Stability Study:

(b) (4)

(b) (4)

e) Statistical analysis of stability data at +25°C (b) (4)

(b) (4) batches at all dosage strengths were included. The following stability data were analyzed: 250 IU from 12 to 24 months, 500 IU up to 18 months, 1000 IU from 12 to 36 months, 2000 IU from 12 to 30 months for FDP stored at +25°C (b) (4)

The analysis parameters and specification accept criteria were:

Factor IX activity: (b) (4)

(b) (4)

Residual moisture: (b) (4)

(b) (4)

Statistical analysis:

Analysis of covariance combining batches of all strengths:

Expanded two-sided 95% confidence intervals (based on classical one-sided 95% confidence limits) for the mean values at any time

Results:

All measured values were within specification.

For all analyzed variables, the expanded two-sided 95% confidence intervals stayed within specification for a minimum of 24 months. Regarding the 1000 IU and 2000 IU batches, the 95% confidence intervals stayed within specification (b) (4).

Reviewer's Comments: The variables analyzed in this report support a tentative shelf-life of 24 months for all dosage strengths of FDP when stored at +25°C, moreover, for the 1000 IU and 2000 IU dosage data support a shelf-life of 36 months at +25°C.

Reviewer's conclusions for FDP stability studies:

An overview of all test results of stability parameters for the pilot and commercial scale batches support that (1) for 250 and 500 IU dosage strengths, the FDP is stable for up to 24 months when stored at +5 °C and +25 °C; (2) for 1000 and 2000 IU dosage strengths, the FDP is stable for up to 36 months when stored at +5 °C and +25 °C.

Several studies were initiated to investigate FDP stability including pilot scale, engineering and GMP batches. All data were within the specification acceptance criteria when stored at +5 to +25 °C with a few insignificant outliers when stored at +25°C. A statistical analysis was performed to analyze the data at +25°C ($\pm 2^\circ\text{C}$) (b) (4). The analysis indicated that there is no significant difference between all measured values. In the (b) (4)

content were observed. These phenomena were to be expected under stress conditions. The FDP should not be kept under stress conditions.

4. Stability Study for sterile Water for Injection

a) Materials

(b) (4) lots of sWFI ((b) (4) lots each of filling sizes 2.5 mL and 5 mL) were used in stability studies and were monitored at defined time intervals.

b) Primary packaging material

Container: 2.5 mL and 5 mL: 6 mL injection vial, glass (b) (4)

c) Specifications for sWFI

Table 3: Test parameters, methods and corresponding specifications

(b) (4)

d) sWFI Storage Conditions

- (b) (4)

e) Stability Study Results:

(b) (4)

Reviewer's comments: All test results met the specifications indicating that sWFI is stable at (b) (4) (b) (4), supporting the sWFI shelf life at (b) (4).

5. Conclusion & Recommendation

I recommend approval of this BLA because the data from the stability studies for BDS, FDP and sWFI are acceptable and support the proposed shelf-life as follows:

- BDS for (b) (4)
- FDP 250 IU and 500 IU dosage for 24 months at +5°C (±3°C) to +25°C (b) (4) protected from light. FDP 1000 IU and 2000 IU dosage for 36 months at +5°C (±3°C) to +25°C (b) (4), protected from light.
- The reconstituted FDP must be used immediately or within 4 hours after reconstitution.
- The shelf life of sWFI is (b) (4) (b) (4)

Under these storage conditions, there is no impact of storage on the (b) (4) and quality of IDELVION BDS and FDP, and sWFI within the proposed shelf-life.

- The BDS stability data (b) (4) of IDELVION BDS batches are consistently within their specification indicating that there is no significant variability in IDELVION (b) (4) in different batches. In addition, the data also indicated that the (b) (4) in IDELVION were within specification with (b) (4) over time.
- All stability results of IDELVION FDP in pilot and commercial scale batches support that the 250 and 500 IU dosage strengths are stable for up to 24 months when storage at +5 °C and +25 °C; for 1000 and 2000 IU dosage strengths are stable for up to 36 months when stored at +5 °C and +25 °C. Several stability studies of IDELVION FDP were performed, all the data were within the specification acceptance criteria when stored at +5 °C, as well as +25 °C. The statistical analysis of stability data for storage at +25°C ($\pm 2^{\circ}\text{C}$) / (b) (4) support that the IDELVION FDP is stable when stored at +25°C (b) (4)
- sWFI pre-filled syringes were studied under different storage conditions, the data support the proposed shelf-life and demonstrate consistent quality.